~~17-39. (Canceled)~~

7 ~~40~~. (Amended) The method of claim 5 ~~15~~, wherein the disease or condition is an autoimmune disease and which is rheumatoid arthritis, lupus, multiple sclerosis and ulcer.

8 ~~41~~. (Previously Presented) The method of claim 1, wherein the composition modulates LPS-induced cytokine production.

9 ~~42~~. (Amended) The method of claim 1 or 2 ~~3~~, wherein the animal is a human.

STATUS AFTER DECISION ON APPEAL AND DECISION ON REHEARING

After the Hearing of March 6, 2008 and the Decision On Request For Rehearing of November 5, 2008, the rejection of claims 1-9 under 35 U.S.C. § 112 first paragraph, as drawn to new matter, is reversed. The rejection of claims 1-9 under 35 U.S.C. § 102(e), as anticipated by Wang is reversed. The rejection of claims 1-9 35 U.S.C. § 112 first paragraph, as lacking enablement, is affirmed. The rejection of claims 1-9 under 35 U.S.C. § 102(e) as anticipated by Reuben is affirmed. The Board has acknowledged that SEQ ID NO: 478 is different from SEQ ID NO: 2 (DRR p. 4).

REMARKS /ARGUMENTS

A. The first objection remaining is whether Claims 1-9 are sufficiently described in the specification so as to be enabled under the meaning of 35 U.S.C. § 112, first paragraph.

The Board has agreed that the specification are enabling and that there is no need of undue experimentation for administering a composition comprising a soluble peptide containing a portion of amino acid 1-136 of SEQ ID NO:2 to modulate an immune response in vivo (Decision p.13). The Board disagrees with respect to a polypeptide mimetic thereof

of SEQ ID NO: 2 (Decision p. 12 and 13 and DRR p.4). We have amended claim 1 by deleting the language "polypeptide mimetic".

In addition, we have amended claim 1 to include all of SEQ ID NO: 2 to be in exact conformity with our specifications. We have amended claim 2 to be in exact conformity with our specifications as found in parag. [0055] and we quote "A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions, fusions and truncations, which may be present in any combination." We have amended claims 3-7 and 9 to be in accordance with the renumbering of the claims. And we have amended claim 7 to be complete and according to our specification parag. [0033].

B. The second objection remaining is whether Claims 1-9 are anticipated by the disclosures of U.S. patent no. 6,420,526 by Reuben under the meaning of 35 U.S.C. § 102(e).

The applicants believe that Claims 1-9 are not anticipated by the disclosures of US patent no. 6,420,526 by Reuben for the following reasons.

1) The two molecules have different sequences and thus are not the same. A basis of the rejection is the apparent similarity of the sequence SEQ ID NO: 478 and SEQ ID NO: 2 of this application. The Board has acknowledged the difference (DRR p.4) while still missing an important point. SEQ ID NO: 2 from Applicants' specification is found in Figure 4 and is defined as being the amino acid sequence of TREM-1sv as defined in specifications [56] and [60]. More specifically in Figure 4, TREM-1sv is the lower amino acid sequence presented. It contains only 150 amino acids because of a deletion from amino acid 136 to 200 that is coding for the transmembrane portion of TREM-1. Moreover, it has a distinct addition of 15 amino acids from 136 to 150. This sequence with the deleted portion and a new addition corresponds to TREM-1sv and is SEQ ID NO: 2. Reuben's SEQ ID NO: 478

contains 234 amino acids because it does not contain this deletion (see APPENDIX II, Reuben's SEQ ID NO: 478) and does not contain the distinct addition of SEQ ID NO: 2. It is similar to the TREM-1 sequence or the upper sequence of amino acids presented in Figure 4. Sequence comparison between SEQ ID NO: 2 or TREM-1sv and Reuben's SEQ ID NO: 478 or TREM-1 shows that SEQ ID NO: 2 has a composition different from Reuben's, making it a different molecule with different property and use as well.

2) The method of use in each invention is different. The present invention teaches the administration of a composition of soluble polypeptides whereas Reuben's invention teaches the administration of a polypeptide. Administering a polypeptide versus administering a soluble polypeptide is significantly different as shown by the mechanism of action of each invention that is distinct. Reuben's method would not work in the present invention. In our method, we administer a composition of soluble polypeptides to capture TREM-1 ligand because there is a requirement for solubility of the polypeptide for this mechanism to work. As recognized by the Board, Reuben did not identify that mechanism (DRR p.5) and consequently his method is not adequate to fulfill the characteristic TREM-1 ligand binding modulation of the immune system. In order to do so, the polypeptide must be soluble to travel in the body and capture the ligand before it reaches TREM-1 as described in our specification parag. [101]. If the polypeptide is not soluble it will not bind TREM-1 ligand and it won't travel to find that ligand. Therefore, there can be no anticipation that Reuben's peptides can fulfill that purpose because the solubility requirement present in our method as well as the teaching of modulating the immune response through the TREM-1 pathway are absent from Reuben's specification.

3) The immunological mechanism targeted by the method used in each invention is different.

Reuben claims a series of EST sequences of which he claims that administration of their correspondent peptides can modulate the immune system through the antigen-antibody network of immune regulation involving T cells. In contrast, Applicants claim invention of a therapeutic method including the use of a composition of soluble peptides according to sequence of SEQ ID NO: 2 for modulating the immune system specifically through the monocyte TREM-1 receptor ligand binding activity.

Reuben teaching is based on similarity with the heavy chain of immunoglobulin (Ig) and their binding function as stated in Decision, FF19. Igs have been known to bind a wide variety of antigens long before Reuben and this is a teaching different from the one of the distinctive macrophage receptor of activation TREM-1 binding to its specific ligand such as the teaching of Applicant's specification. Reuben does not teach anything in regard to the TREM-1 receptor ligand complex but rather antigens binding to antibody-like structure. Second and not the least, Reuben's specification column 139 in "Feature of Protein Encoded by Gene No: 159 "teaches that "This gene is expressed primarily in activated neutrophil and to a lesser extent in activated T cell, monocytes, and heart." The Applicants' invention teaches that TREM-1 receptor is expressed exclusively on myeloid cells, defined as being macrophages and neutrophils (Applicants' specification paragraph [6]). TREM-1 receptor is not on T cells, defined as lymphoid cells and is not on heart cells as both thought by Reuben. Exclusive expression on myeloid cells is the reason for the origin of its name TREM-1 (Triggering Receptor Expressed on Myeloid-1) as defined by Bouchon et al., in REFERENCES of the specification. Moreover, the Applicants teach that the specific complex TREM-1 receptor-ligand is known to trigger the TREM-1 receptor present on macrophages and to activate them. And the binding of TREM-1sv or a soluble peptide with the same biological binding activity to that specific TREM-1 ligand can modulate the immune response through macrophage regulation of activation. In contrast, Reuben teaches

a molecule with the natural binding activity of Ig that can bind a large variety of common antigens that may modulate the immune response through the antigen-antibody network of immunoregulation. He does not teach regulation of the immune system through the macrophage TREM-1 ligand complex-receptor. In that respect, using a composition of soluble polypeptides such as in the present invention versus Reuben's administration of a peptide where there is no teaching of requirement for solubility are two different inventions because Reuben's method as described in his specifications would not work through the TREM-1 pathway. Evidently, each method is different because it targets a different mechanism of action. And distinction between the teachings and methods of each invention is supported by the fact that there is neither data nor evidence that TREM-1 ligand is a common antigen. In fact, recent data suggest that it is a receptor expressed by platelets (Haselmayer et al. Blood 110:1029, 2007, copy enclosed) supporting our point that this invention's teaching of the specific TREM-1 receptor and TREM-1sv ligand binding activity is substantially different from Reuben's anticipated molecule with Ig like binding activity for a variety of common antigens and which is expressed also on T cells.

In that regard, the Applicants claim and present validation of biological activity for soluble portion of sequence of SEQ ID NO: 2 and for its usage in the treatment of conditions that can benefit from capturing that specific TREM-1 receptor binding ligand with TREM-1sv or derived peptides before it reaches the myeloid expressed TREM-1 activating receptor. The Applicants state that their specification and claims are the results of experimentations conducted that lead to the discovery of TREM-1sv (specification, Figure 2 and also Gingras et al., Molecular Immunology 38:817, 2001, copy enclosed) and they assert that their specification teaches a distinct method involving administration of a soluble polypeptide to modulate the immune system, that is not anticipated nor described by Reuben's, for the

treatment of conditions that can benefit from capturing the specific TREM-1 receptor binding ligand.

Therefore, based on the facts that 1) SEQ ID NO: 498 and SEQ ID NO: 2 are two different molecules, 2) the method of use of each invention is different as evidenced by their respective targeted mechanism of immune modulation and 3) the mechanism of immune modulation targeted by each invention is distinct, the Applicants believe that the rejection anticipated by Reuben should be reversed.

CONCLUSION

The Applicants believe that in light of the new amendments and of the above clarifications about the difference between the two inventions, the remaining rejections are overcome and the application now meets condition of allowance.

Respectfully submitted,

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